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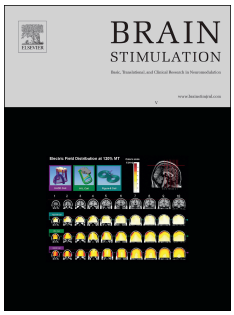

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PII: S1935-861X(18)30078-0

DOI: 10.1016/j.brs.2018.02.015

Reference: BRS 1203

To appear in: *Brain Stimulation*

Received Date: 19 September 2017

Revised Date: 6 February 2018

Accepted Date: 22 February 2018

Please cite this article as: Dafsari HS, Weiß L, Silverdale M, Rizos A, Reddy P, Ashkan K, Evans J, Reker P, Petry-Schmelzer JN, Samuel M, Visser-Vandewalle V, Antonini A, Martinez-Martin P, Ray-Chaudhuri K, Timmermann L, On behalf of EUROPAR and the IPMDS Non Motor PD Study Group, Short-term quality of life after subthalamic stimulation depends on non-motor symptoms in Parkinson's disease, *Brain Stimulation* (2018), doi: 10.1016/j.brs.2018.02.015.

Brain Stimulation (Original Article)

Short-term quality of life after subthalamic stimulation depends on non-motor symptoms in Parkinson's disease

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Character count title: 109
Number of references: 47
Number of tables: 2
Number of figures: 2
Word count abstract: 249/250
Word count text: 3541/4000
Supplemental Data: Supplemental table A, Supplemental material file A

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Search terms: Deep brain stimulation; Subthalamic nucleus; Non motor symptoms; Parkinson's Disease Questionnaire

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K. Ray Chaudhuri, study concept and design, critical revision of manuscript
Lars Timmermann, study concept and design, critical revision of manuscript

Financial disclosure/Conflicts of interest:

Haidar S. Dafsari’s work was funded by the Prof. Klaus Thiemann Foundation and the Felgenhauer Foundation. Jan Niklas Petry-Schmelzer’s work was supported by the Koeln Fortune Program.
This paper is independent research funded by the German Research Foundation (Grant KFO 219), the National Institute of Health Research (NIHR) Mental Health Biomedical Research Centre and Dementia Unit at South London and Maudsley NHS Foundation Trust and King’s College London. Additionally an unrestricted peer reviewed educational grant was provided to support coordination of the UK dataset from Medtronic.

Haidar Salimi Dafsari has received honoraria by Boston Scientific and Medtronic.
Luisa Weiss reports no disclosures.
Monty Silverdale has received honoraria has received honoraria from Bial, Britannia and Medtronic.
Alexandra Rizos has received honorarium from UCB and was supported by a grant from Medtronic.
Prashanth Reddy reports no disclosures.
Keyoumars Ashkan has received honoraria for educational meetings, travel and consultancy from Medtronic, St Jude Medical and Boston Scientific.
Julian Evans reports no disclosures.
Paul Reker reports no disclosures.
Jan Niklas Petry-Schmelzer reports no disclosures.
Michael Samuel has received honoraria for educational meetings/travel/ accommodation from Medtronic, St Jude Medical, and UCB, grants from Parkinson's UK and Ipsen, and has acted as a consultant for Medtronic and St Jude Medical.

Veerle Visser-Vandewalle is a member of the advisory boards and reports consultancies for Medtronic, Boston Scientific and St Jude Medical. She received a grant from SAPIENS Steering Brain Stimulation.
Angelo Antonini reports personal consultancy fees from Sunovion, Zambon, AbbVie, Angelini, UCB, Boehringer Ingelheim, Cynapsus Therapeutics, GE, Medtronic, Boston Scientific, Mundipharma, Ever Neuro Pharma, grants from Horizon2020 Project No 643706, owns Patent WO2015110261-A1, owns shares from PD Neurotechnology Limited
Pablo Martinez-Martin has received honoraria from Editorial Viguera and Movement Disorder Society for lecturing in courses; from AbbVie for speaking in experts’ meetings and for participating in the Advisory Board of an epidemiological study, and grants from the International Parkinson and Movement Disorder Society for the Pilot Study of the MDS-Non-Motor Symptoms Scale.
K. Ray Chaudhuri has received funding from Parkinson's UK, NIHR, UCB, and the European Union; he received honoraria from UCB, Abbott, Britannia, US Worldmeds, and Otsuka Pharmaceuticals; and acted as a consultant for AbbVie, UCB, and Britannia.
MiS has received honoraria for educational meetings/travel/accommodation from Medtronic, St Jude Medical, and UCB, grants from Parkinson's UK and Ipsen, and has acted as a consultant for Medtronic and St Jude Medical.
Lars Timmermann reports grants, personal fees and non-financial support from SAPIENS Steering Brain Stimulation, Medtronic, Boston Scientific and St. Jude medical

Glossary: CI = confidence interval; **DBS** = deep brain stimulation; **HADS** = Hospital Anxiety and Depression Scale; **NMS** = Non-motor symptoms; **NMSS** = NMSScale; **NMSQ** = NMSQuestionnaire; **OR** = odds ratio; **PD** = Parkinson’s disease; **PDQ-8** = 8-item PD Questionnaire; **QoL** = quality of life; **SCOPA-A, -B, and -C** = Scales for Outcomes in PD-motor examination, -activities of daily living, and -motor complications; **STN** = subthalamic nucleus

Abstract

Background: Subthalamic nucleus (STN) deep brain stimulation (DBS) improves quality of life (QoL), motor, and non-motor symptoms (NMS) in advanced Parkinson’s disease (PD). However, considerable inter-individual variability has been observed for QoL outcome.

Hypothesis: We hypothesized that demographic and preoperative NMS characteristics can predict postoperative QoL outcome.

Methods: In this ongoing, prospective, multicenter study (Cologne, Manchester, London) including 88 patients, we collected the following scales preoperatively and on follow-up 6 months postoperatively: PDQuestionnaire-8 (PDQ-8), NMSScale (NMSS), NMSQuestionnaire (NMSQ), Scales for Outcomes in PD (SCOPA)-motor examination, -complications, and –activities of daily living, levodopa equivalent daily dose. We dichotomized patients into “QoL responders”/“non-responders” and screened for factors associated with QoL improvement with (1) Spearman-correlations between baseline test scores and QoL improvement, (2) step-wise linear regressions with baseline test scores as independent and QoL improvement as dependent variables, (3) logistic regressions using aforementioned “responders/non-responders” as dependent variable.

Results: All outcomes improved significantly on follow-up. However, approximately 44% of patients were categorized as “QoL non-responders”. Spearman-correlations, linear and logistic regression analyses were significant for NMSS and NMSQ but not for SCOPA-motor examination. Post-hoc, we identified specific NMS (flat moods, difficulties experiencing pleasure, pain, bladder voiding) as significant contributors to QoL outcome.

Conclusions: Our results provide evidence that QoL improvement after STN-DBS depends on preoperative NMS characteristics. These findings are important in the advising and selection of individuals for DBS therapy. Future studies investigating

motor and non-motor PD clusters may enable stratifying QoL outcomes and help predict patients’ individual prospects of benefiting from DBS.

1. Introduction

Subthalamic nucleus (STN) deep brain stimulation (DBS) is well established as a treatment option for advanced Parkinson’s disease (PD) improving motor symptoms [1], quality of life (QoL) [2] and non-motor symptoms (NMS) [3] on a group level. However, studies investigating outcomes on the subject level indicate that a considerable proportion of patients (between 43-49%) do not experience a relevant QoL improvement after STN-DBS [4, 5]. Data on the preoperative determinants QoL outcome are scarce and suggest a role of some motor aspects, such as long daily off time [4] or small levodopa challenge test response [6], as well as some neuropsychiatric factors, such as high apathy scores [7]. In the present study, we therefore conducted a comprehensive assessment of a wide range of non-motor and motor symptoms to explore predictors of beneficial QoL outcome after STN-DBS. We hypothesized that NMS can predict QoL outcome after DBS.

2. Methods

2.1. Study design

In this ongoing, prospective, open-label, multicenter, international study (Cologne, London, Manchester) we examined patients with PD undergoing bilateral implantation of stimulation electrodes for STN-DBS in the DBS arm [3] of the EuroInf study at preoperative baseline and follow-up 6 months after surgery. Data from 35 patients was included in a previous analysis published by our group on beneficial non-motor effects of STN-DBS in a large cohort of patients with PD [3].

2.2. Ethical approval

The study was carried out in accordance with the Declaration of Helsinki and approved by local ethics committees (Cologne, study no.: 12–145; German Clinical Trials Register: DRKS00006735; United Kingdom: NIHR portfolio (Clinical Research Network) number: 10084; National Research Ethics Service South East London REC 3, 10/H0808/141). Patients gave written informed consent prior to study procedures.

2.3. Patients

All patients fulfilled British Brain Bank PD diagnosis criteria and DBS treatment criteria of the International PD and Movement Disorders Society [8]. According to clinical routine, an eligibility for DBS treatment required a sufficient levodopa test response (>30% improvement in the Unified Parkinson’s Disease Rating Scale-III) and an exclusion of clinically relevant cognitive impairments and psychiatric diseases in assessments by expert neuropsychologists and psychiatrists.

2.4. Clinical assessment

The following scales and questionnaires were assessed, as previously reported in the EuroInf study [3, 9, 10]. All scales were assessed preoperatively in a clinical MedON- and postoperatively in a clinical MedON/StimON-state.

2.4.1 Quality of life

QoL was assessed with the PD Questionnaire-8 (PDQ-8) [11] which has previously been used for patients with PD and STN-DBS [12, 13]. The PDQ-8 surveys the frequency of the following eight aspects of QoL: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, bodily

discomfort. The score ranges from 0 to 32 (no to maximum QoL impairment). PDQ data is presented as PDQ-8 Summary Index (PDQ-8 SI) [3, 12, 14].

2.4.2 Non-motor symptoms

As the following non-motor scales assessed a time period of the previous four weeks before surveying, they reflected ON and OFF times.

- The patient-based NMS Questionnaire (NMSQ) wich consists of 30 dichotomized items. NMSQ total score ranges from 0 (no NMS) to 30 (maximum NMS) [15].
- The clinician-administered NMS Scale (NMSS) consisting of 30 items covering nine domains of NMS: cardiovascular, sleep/fatigue, mood/apathy, perceptual problems/hallucinations, attention/memory, gastrointestinal tract, urinary, sexual function, and miscellaneous (including unexplained pain, taste/smell loss, weight changes, and sweating). NMSS total score ranges from 0 (no NMS) to 360 (maximum NMS) [16].
- The Hospital Anxiety and Depression Scale (HADS) which consists of subscales testing anxiety and depression with seven items respectively. Subscales range from 0 (no anxiety/depression) to 21 (maximum anxiety/depression) [17].

2.4.3 Motor manifestation

Motor examination, activities of daily living, and motor complications were assessed with Scales for Outcomes in Parkinson’s disease (SCOPA-A, -B, -C) which strongly correlate to the UPDRS and were derived from this scale [18]. The SCOPA was used for time economic reasons as its assessment time is approximately 4 times shorter than for the MDS-UPDRS [18-20].

2.4.4 Levodopa-equivalent daily dose

We computed the levodopa-equivalent daily dose according to the Tomlinson method [21].

2.5. Statistical analysis

2.5.1 Changes of outcome parameters from baseline to follow-up

Normal distribution was tested with the Shapiro-Wilk-test and outliers (>3 SD) were truncated to the next highest value. Test score changes from baseline to follow-up were detected with the Wilcoxon signed-rank test or paired t-test, when parameteric test criteria were fulfilled, and Bonferroni-correction for multiple comparisons.

We explored the relationship between preoperative demographic and clinical features and QoL outcome in the following analyses.

2.5.2 Relationship between baseline quality of life and changes of other outcomes

a. Spearman-correlation analyses

Spearman-correlations were computed between PDQ-8 SI change scores (PDQ-8 $SI_{baseline}$ – PDQ-8 $SI_{follow\text{-}up}$) and preoperative QoL (PDQ-8 $SI_{baseline}$), non-motor ($NMSS_{baseline}$, $NMSQ_{baseline}$, $HADS_{baseline}$) and motor symptoms (SCOPA-motor $examination_{baseline}$, -motor $complications_{baseline}$, -activities of daily $living_{baseline}$), levodopa equivalent daily $dose_{baseline}$ and demographic characteristics (age at intervention, disease duration, sex). Positive correlations reflect an association between higher baseline values of respective parameters and more PDQ-8 SI improvement. Due to the exploratory character of this analysis, significance

thresholds were not corrected for multiple comparisons. Results were accepted as significant at $p<0.05$.

b. Predictor analysis

Secondly, to identify preoperative predictors of postoperative QoL outcome, stepwise linear regressions were computed for candidate parameters identified in step one. In this step, candidate parameters from the correlation analyses ($p<0.1$) were included and multi-collinearity was checked ($r>0.6$).

c. Dichotomization into “responders“/“non-responders“ and logistic regression analyses

We divided the cohort into groups with and without clinically relevant QoL improvement (“responders”/“non-responders”) based on a designated threshold (≥½ SD of PDQ-8 $SI_{baseline}$) [3] which is a method that has been shown to reliably report clinically important differences [22]. We then calculated the proportion of “responders” based on this threshold.

Exploratory logistic regression models with dichotomized QoL outcome as dependent and demographic factors and preoperative clinical parameters as independent variables were employed to confirm the utility of linear regression models to predict patients’ postoperative QoL changes. Additionally, Mann-Whitney U tests were computed to confirm $Test_{baseline}$ differences between “responders”/“non-responders”.

d. Exploratory analyses of NMSS item scores

As we were interested in the relationship of QoL changes and specific aspects of NMS, all analyses were also carried out for NMSS item scores.

Due to an overlap between specific PDQ-8 and NMSS questions (see supplemental material section 1), additionally all calculations were confirmed with a modified PDQ in which respective items were omitted for calculations with corresponding NMSS items.

3. Results

Our study included 88 patients with PD (56 male) with mean age at intervention=61.2 years (SD=8.1) and disease duration=10.5 years (SD=4.5). Here we present data from 30 patients from Manchester, 22 patients from London, and 36 patients from Cologne. The mean time to follow-up from surgery was 5.49 months (SD=0.86).

3.1. Changes of outcome parameters from baseline to follow-up

All outcome parameters significantly improved on follow-up (see table 1). As PDQ-8 SI significantly improved, we explored changes of its domain scores: All domains, except ‘Cognition’, improved significantly (see figure 1 and supplemental table A).

3.2. Relationship between baseline quality of life and changes of other outcomes

a. Spearman-correlation analyses

Table 2 shows the results of Spearman-correlations with preoperative test scores/demographic variables and PDQ-8 SI change scores. Foremost, a significant correlation was observed between baseline PDQ-8 SI score and postoperative PDQ-8 SI improvement. Other significant correlations were weak (NMSS, NMSQ, and SCOPA-B).

b. Predictor analysis

Using stepwise linear regression analyses including aforementioned preoperative demographic and clinical parameters, we identified predicting factors for the QoL outcome. The resulting model accounted for 42.6% (R^2=0.446) of the variance in QoL change ($F_{3,84}$=22.53, p<0.001). It included PDQ-8 SI (β=0.508, p<0.001), NMSS items 12 (“difficulties in experiencing pleasure”, β=0.268, p<0.005) and 23 (“high voiding frequency”, β=0.152, p<0.01).

c. Dichotomization into “responders“/“non-responders“ and logistic regression analyses

Based on the above mentioned cohort-based cut-off, the calculated threshold for a relevant PDQ-8 SI improvement was 8.22. In our cohort (87 patients with valid pre- and postoperative PDQ scores), 56.3% (n=49) of patients were identified as “QoL responders” and 43.7% (n=38) as “non-responders” and 16.1% (n=14) reported a relevant QoL worsening (deterioration≥½ SD of PDQ-8 $SI_{baseline}$).

In logistic regressions exploring demographic parameters, we found that every additional year of age at intervention decreased the odds of postoperative QoL improvement by approximately 6% (odds ratio [OR]=0.944, confidence interval [CI]=0.891–0.999, p=0.047). Female sex was associated with higher odds of beneficiary postoperative QoL outcome (OR=2.626, CI=1.030 – 6.695, p=0.043). The odds of QoL improvement were increased for every additional point on the PDQ-8 $SI_{baseline}$ by approximately 5% (OR=1.051, CI=1.017–1.086, p=0.003), for every point on the NMSQ total $score_{baseline}$ by approximately 13% (OR=1.132, CI=1.027–1.248, p=0.012), and for every 10 points increase on the NMSS total $score_{baseline}$ by 16% (OR=1.016, CI=1.002–1.030, p=0.030). Mann-Whitney U tests confirmed significant

differences for the above mentioned parameters: PDQ-8 $SI_{baseline}$ (p=0.007), NMSQ total $score_{baseline}$ (p=0.012), and NMSS total $score_{baseline}$ (p=0.037).

d. Exploratory analyses of NMSS item scores

Furthermore, specific NMSS items had a significant predicting potential:

One extra point in NMSS item $11_{baseline}$ (“flat moods”) raised the probability of a positive QoL outcome by approximately 74% (OR=1.739, CI=1.070–2.827, p=0.025), in item $27_{baseline}$ (“pain”) by approximately 14% (OR=1.141, CI=1.010–1.288, p=0.034) and in item $29_{baseline}$ (“weight changes”) by 27% (OR=1.270, CI=1.026–1.572, p=0.028).

In out cohort complete sets of predictor and outcome variables was available in 83 patients. A fitted logistic regression model incorporating the aforementioned parameters: age at intervention, PDQ-8 $SI_{baseline}$, NMSQ total $score_{baseline}$, and NMSS item $11_{baseline}$ correctly classified 68.7% of patients into groups of “QoL responders”/”non-responders” (57/83, Nagelkerke’s R^2=0.291) as opposed to only 57,8% without predictors (48/83). In other words, the assessment of basic demographic features and clinical scales significantly increased the predictive accuracy of QoL response classification by approximately 10%. The receiver operating characteristic curve for the fitted logistic regression demonstrated the discriminatory power of the model (C-statistic=0.77, p<0.001, CI=0.668–0.873, see figure 2) [23] which reached 79.2% sensitivity and 62.9% specificity at the optimal trade-off point.

For the most part, linear and logistic regression results were also confirmed in the Mann-Whitney U tests comparing baseline characteristics of “responders”/“non-

responders”. “Responders” had significantly higher $Test_{baseline}$ values for NMSS item 11 (“flat moods”, p=0.005), item 12 (“difficulty experiencing pleasure”, p=0.001), item 27 (“pain”, p=0.027), item 29 (“weight changes”, p=0.018).

The results of additional analyses adressing the overlap of NMSS and PDQ-8 items are reported in the supplemental material A section 2.

4. Discussion

In this prospective, open-label, multicenter, international study including a cohort of 88 patients with PD, STN-DBS significantly improved QoL, motor and non-motor outcomes as well as medication requirements on 6 months follow-up after surgery. However, we observed considerable inter-individual variance as only 56.3% of patients experienced a clinically relevant improvement of QoL (“QoL responders”). The remaining 43.7% of patients were to be classified as “QoL non-responders”, a rate well within the range of other cohorts (41–49%) [4, 5]. To address the unmet need of identifying factors which contribute to this high inter-individual variance, we evaluated the non-motor, motor, and demographic predictors of QoL outcome:

4.1. Non-motor predictors of quality of life

As a key finding of our study, we observed that preoperative non-motor aspects of PD, i.e. “difficulties in experiencing pleasure” and “high frequency of voiding”, were significant predictors of QoL outcome and together with preoperative QoL explained 42.6% of the variance of postoperative QoL change. Furthermore, specific NMS (“flat moods”, “weight changes” and “pain”), global NMS burden, QoL at baseline, and demographic factors had a significant predictive value for the QoL outcome.

We explored not only preoperative QoL and motor symptoms but also NMS as potential predictors of QoL outcome because of the emerging concept of non-motor effects of DBS [24, 25]. This concept is based on evidence from comprehensive assessments with clinician-based and self-reported patient-based scales, e.g. for depressive symptoms [26], pain [27], sleep [28], gastrointestinal symptoms, excessive sweating, and perceptual problems/hallucinations [3], and also backed by a growing number of studies using laboratory-assisted objective measures for specific NMS, e.g. polysomnography for sleep [29], $^{13}CO_2$ excretion for gastric emptying [30], urodynamic examination for urinary symptoms [31], caloric chambers for daily energy expenditure/weight changes [32], and sympathetic skin response for excessive sweating [33]. Furthermore, our previous work has provided evidence that patients with stronger postoperative improvement of NMS experience significantly more QoL improvement [3].

To understand the predictive potential of specific NMS for QoL outcomes in DBS several factors may be important:

1. The strong link between QoL and NMS in PD is well known [34, 35]. As specific NMS are amenable to DBS their alleviation potentially also improves QoL. In this context the following mechanisms may play a role: Mood [36, 37] could be affected by a modulation of associative basal ganglia-thalamo-cortical loops and autonomic symptoms like bladder control [31] and pain [27] by limbic circuitry. Furthermore, local effects may play a role, i.e. via the spread of current to brain brain regions next to the STN: The lateral hypothalamus could, e.g., be modulated which may result in weight changes [38].

2. An improvement of sensory gaiting/processing: Previous studies have provided evidence that this PD-related pathopysiological mechanism is amenable to DBS but not necessarily to dopaminergic medication, e.g., in specific types of pain [39], bladder control [31] and auditory deficits [40]. Therefore, high preoperative severities of these NMS may be a surrogate marker for beneficial NMS outcome which may result in beneficial QoL outcome.
3. Neuropsychiatric symptoms, such as depression and anxiety, are particularly important for DBS outcomes. A failure to improve in these symptoms can diminish subjective QoL outcome [7]. Consistent with findings from previous studies [5, 7], step-wise linear regressions showed that more improvement of “flat moods” and “difficulties experiencing pleasure” is an important determinant of more QoL improvement. One has to acknowledge that, unlike these NMSS items, HADS total scores did not predict QoL outcomes in our cohort. This discrepancy may result from the fact that these items flat moods and difficulties experiencing pleasure are more specific, whereas HADS total scores summarize a wider range of anxiety and depression symptoms.
4. The reduction of non-motor and motor fluctuations due to the continuous effects of DBS may play an important role. Previous studies have provided evidence for an improvement of non-motor fluctuations of depressive mood and bladder urgency by DBS [41]. Furthermore, weight changes may stabilize in a subset of patients as a reduction of, e.g., dykinesia, rigidity and tremor resulting from motor fluctuations may alleviate excessive energy expenditure [42]. We found a predictive potential for QoL improvement in all these symptoms.

4.2. Predictive value of preoperative quality of life, motor and demographic parameters

4.2.1 Preoperative quality of life

In line with previous results [5, 43], we found that higher preoperative QoL impairment is a significant predictor of more postoperative QoL improvement. As regards the relationship between preoperative PDQ scores and postoperative PDQ outcomes our result of an OR=1.05 remarkably resembles results of the Cleveland Clinic cohort (same OR=1.05). In line with previous studies, we observed no improvement of the cognition domain [2, 5]. The confirmation of these results in an independent cohort emphasizes the validity of our results and the high test-retest validity of the PDQ [5].

4.2.2 Preoperative motor manifestation

In line with previously published studies in other cohorts [4, 5], we observed no significant predictive value of motor examination scores in our cohort. While there were negative results in previous studies regarding a relationship between preoperative UPDRS-III and postoperative QoL outcome, there was, however, evidence for a relationship with the response to dopaminergic medication, either directly (preoperative improvement in the levodopa challenge test) or indirectly (preoperative daily cumulative off time). We did not investigate levodopa response as all patients included in our study were required to fulfill the criterion of >30% UPDRS-III improvement in the levodopa test to be eligible for DBS surgery. Consequently, there is lack of patients with little improvement in the levodopa test and our cohort size was not powered for an analysis of the relationship between levodopa response and QoL outcome after STN-DBS. In fact, a retrospective study

by Floden et al. with a comparable cohort size (85 patients) provided no evidence for this relationship and the authors discussed the above mentioned statistical limitations [5].

4.2.3 Demographic factors

Our results show that higher age at baseline decreases the odds of a beneficiary QoL outcome in patients undergoing STN-DBS. Studies investigating QoL outcomes in DBS have found that age per se may not be a key determinant of QoL, however, it may serve as a surrogate for age-related frailty and co-morbidities which in turn may influence QoL [44]. As regards gender differences, our results are in line with previous studies which have provided evidence for a significantly better QoL outcome in female patients undergoing DBS which may result from more subjective improvement of functional autonomy in women than in men [45].

4.3. Limitations

There are a number of limitations of this study.

As a prospective DBS registry study this was not a randomized or double-blinded study with a best medical treatment control group. However, as a prospective study reliability of data is likely to be better than in retrospective studies and its multicenter design is likely to reduce the potential bias of a single-center design. One has to acknowledge selection bias due to several factors: As per clinical routine patients with dementia or severe depression were not eligible for DBS. Additionally, only patients with motor complications and/or medication-refractory tremor underwent DBS surgery. Consequently, patients with very severe NMS are likely to be

underrepresented in our study which implies limitations for the analysis of NMS predictors of QoL.

Regarding the statistical analysis, the choice of a cut-off value for the classification into “responders”/“non-responders” is a crucial point. Previous studies have employed the same method to derive a cohort-specific cut-off value (≥½ SD of PDQ-8 $SI_{baseline}$) [3, 22]. The calculated cut-off=8.22 in our cohort was similar to a general PD population in which the reliable change index resulted in a cut-off=7.0 on the PDQ-39 SI (10.9 on the PDQ-39 total score) [4]. As the reliable change index is considered to be a conservative method for the calculation of clinically important difference in QoL [4] and our calculated threshold was comparable, we too applied a conservative cut-off for all logistic regression analyses.

As explained in the supplemental material A section 1, there is a considerable overlap between the contents of questions of the PDQ and NMSS which may cause false postive results for the predictor analysis. To minimize this confounding effect, we additionally carried out all analyses with a modified PDQ score in which corresponding PDQ items were left out when respective NMSS items were tested and reincluded for analyses with all other NMSS items. The analyses with this modified PDQ by large confirmed the original results with the unmodified PDQ-8 which increases the reliability of the results (see supplemental material A section 2.1 and 2.2). As regards the motor scales used in the present study, SCOPA scores may offer limited comparability with (MDS)-UPDRS scores assessed in other studies. However, like the MDS-UPDRS the SCOPA is a reliable and valid instrument, the assessment of the SCOPA is approximately four times shorter making the scale more time-efficient, and conversion formulae between these scales are available [18-20].

Although the current work includes one of the biggest cohort sizes in studies of its kind (n=88), increased cohort sizes are required to employ more sophisticated

analyses, such as clustering and a stratification of outcomes. Additionally, assessments of further symptoms, such as impulsivity and apathy, could add value to predictive models [7]. Furthermore, from our relatively short follow-up, we cannot predict which factors contribute to long-term QoL improvement, in particular, as in some patients a relatively long time may be required to find stable effective stimulation parameters or to recover from medication withdrawal. A longer follow-up including neuropsychological and non-dopaminergic NMS as well as axial motor symptoms, such as falls, is required to address the long-term QoL outcome [46, 47]. The non-motor scales employed in this study survey NMS over a time period of four weeks prior to assessment summarizing ON and OFF times and therefore are not feasible to study the microstructure of non-motor fluctuations. An investigation of non-motor OFF times and fluctuations may help to understand the impact of NMS on QoL and to address this issue further studies are needed including non-motor patient diaries.

4.4. Conclusion

The novel findings of this study regarding the predictive value of global and specific NMS for QoL outcome emphasize the importance of a holistic assessment of patients prior to surgery. Future studies investigating preoperative motor and non-motor PD profiles, e.g., with clustering methods, may enable a more precise assessment of patients’ expected postoperative QoL improvement. The overall aim is an individualized advising and better selection of patients for DBS therapy.

Acknowledgments

The authors wish to express their gratitude to patients for their consent and cooperation in this study.

Funding

This paper presents independent research funded by the Prof. Klaus Thiemann Foundation (HSD), the Felgenhauer Foundation (HSD), KölnFortune (JNPS), the German Research Foundation (DFG grant KFO219) and the National Institute of Health Research (NIHR) Mental Health Biomedical Research Centre and Dementia Unit at South London and Maudsley NHS Foundation Trust and King’s College London. Additionally, an unrestricted peer reviewed educational grant was provided to support coordination of the UK dataset from Medtronic.

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***Table 1* – Baseline and follow-up characteristics**

	Baseline			Follow-up			p
	n	**mean**	**SD**	**n**	**mean**	**SD**	
PDQ-8 SI *	88	34.5	16.4	87	23.8	14.4	<0.001
NMSS-T *	86	65.2	34.8	87	45.7	27.5	<0.001
NMSQ-T *	85	11.0	4.9	83	8.1	3.9	<0.001
HADS *	84	11.3	6.1	83	9.0	5.4	<0.001
SCOPA-A *	86	7.8	3.8	83	5.6	2.9	<0.001
SCOPA-B *	87	12.7	6.0	86	8.6	4.7	<0.001
SCOPA-C *	86	5.4	3.0	87	3.0	2.8	<0.001
LEDD *	88	1142.3	512.0	86	636.7	358.1	<0.001

Abbreviations: HADS = Hospital Anxiety and Depression Scale; **LEDD** = Levodopa equivalent daily dose; **NMSS-T** = Non-motor Symptom Scale total score; **NMSQ** = Non-motor Symptoms Questionnaire; **PDQ-8 SI** = Parkinson's Disease Questionnaire-8 items Summary Index; **SCOPA-A, -B, and -C** = Short Outcomes of Parkinson's Disease-motor examination, -activities of daily living, and -motor complications

All scales were assessed in preoperative MedON and postoperative MedON/StimON.

The Bonferroni-correction was employed to correct for type I errors.

* All outcome parameters improved significantly from baseline to follow-up.

***Table 2* – Spearman-correlations between all preoperative scores or demographic variables and postoperative change scores of quality of life**

	Spearman correlation PDQ-8 SI change score		
	n	**rho**	**p**
Age	87	-0.191	0.076
Sex [+]	87	0.150	0.166
Disease duration	87	-0.006	0.959
PDQ-8 SI *	87	0.443	**<0.001**
NMSS-T *	85	0.269	**0.013**
NMSQ-T *	84	0.253	**0.020**
HADS	83	0.131	0.239
SCOPA-A	86	0.080	0.464
SCOPA-B *	85	0.227	**0.037**
SCOPA-C	85	0.059	0.591
LEDD	87	-0.041	0.704

Abbreviations: HADS = Hospital Anxiety and Depression Scale; **LEDD** = Levodopa equivalent daily dose; **NMSS-T** = Non-motor Symptom Scale total score; **NMSQ** = Non-motor Symptoms Questionnaire; **PDQ-8 SI** = Parkinson's Disease Questionnaire-8 items Summary Index; **SCOPA-A, -B, and -C** = Short Outcomes of Parkinson's Disease-motor examination, -activities of daily living, and -motor complications

All scales were assessed in preoperative MedON and postoperative MedON/StimON.

***** Significant correlations between $Test_{baseline}$ or demographic variable and PDQ-8 SI change scores

[+] Rank-biserial correlation

***Figure 1* – PDQ-8 domain scores**

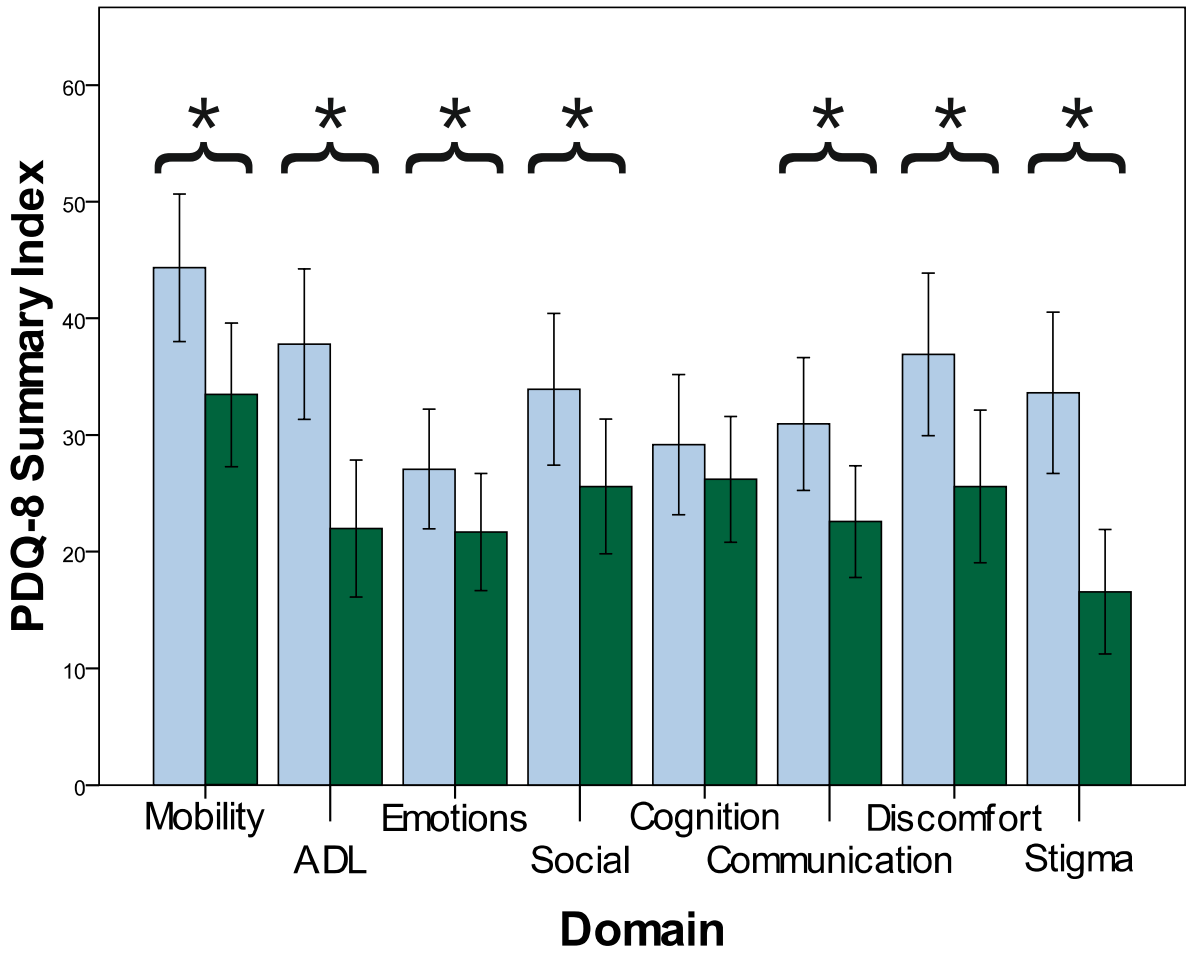

Figure 1 - A Parkinson's disease-specific patient-based self-reported score (PDQ-8) was employed to assess quality of life at preoperative baseline (blue) and follow-up 6 months after surgery (green). Data is presented as Summary Index (=percentage of maximum scores). Mean values of all domains improved from baseline to follow-up. Improvements of all domains were significant (black stars), except for the "Cognition" domain. Black bars illustrate standard deviations. **ADL** = Activities of daily living; **Discomfort** = Bodily discomfort; **Emotions** = Emotional well-being; **PDQ-8** = Parkinson's Disease Questionnaire (8-items version); **Social** = Social support.

***Figure 2* – Regression classification accuracy**

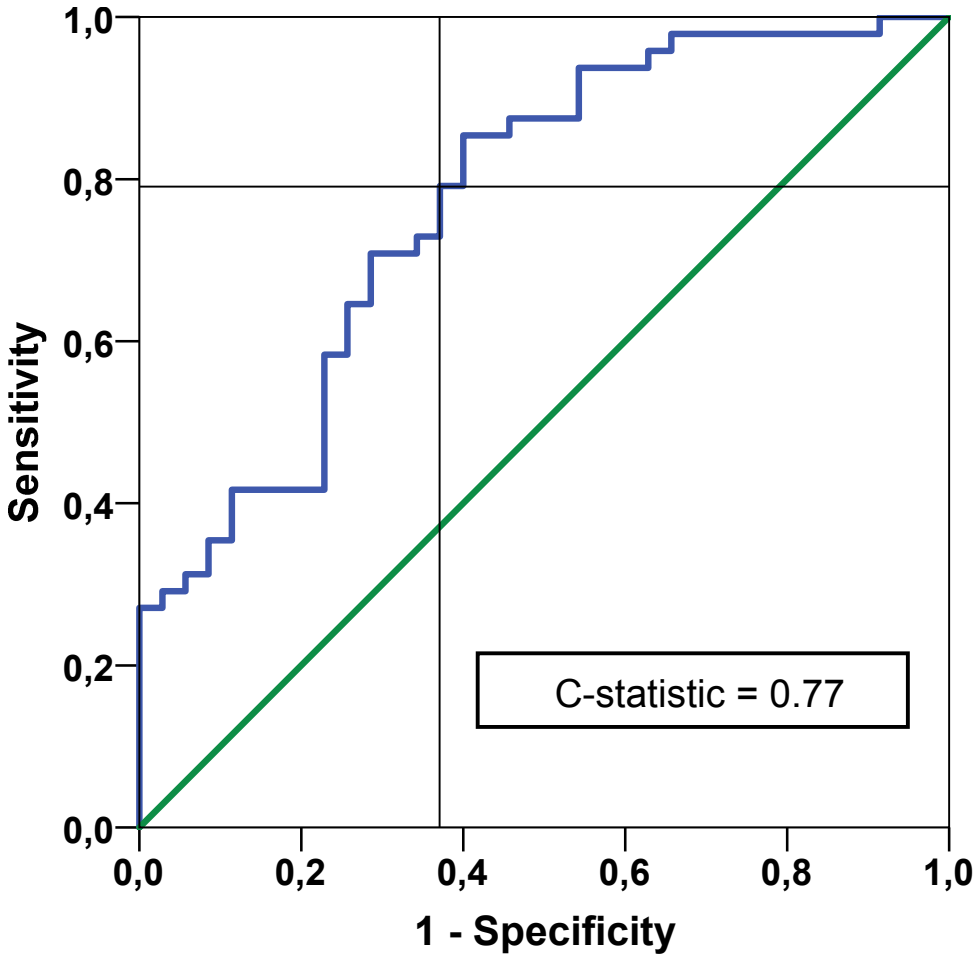

Figure 2 – The receiver operating characteristic curve (blue) illustrates the classification accuracy of the fitted logistic regression model (dependent variable: PDQ-8 SI "responder"/"non-responder", independent variables: age at intervention, PDQ-8 $SI_{baseline}$, NMSQ total $score_{baseline}$, NMSS items $11_{baseline}$). The discriminatory power of the test with these parameters is demonstrated by C-statistic=0.77. The diagonal line (green) represents chance classification accuracy. The cross of black reference lines indicates the optimal trade-off point in which the model reached 79.2% sensitivity and 62.9% specificity.